

Multimodal analgesia as an essential part of enhanced recovery protocols in the ambulatory settings

Alan David Kaye¹, Richard D. Urman², Yury Rappaport³, Harish Siddaiah³, Elyse M. Cornett^{1,3}, Kumar Belani⁴, Orlando J. Salinas¹, Charles J. Fox³

¹Department of Anesthesiology, LSU Health Sciences Center, New Orleans, ³Department of Anesthesiology, LSU Health Shreveport, LA,

²Department of Anesthesiology, Perioperative and Pain Medicine, Harvard Medical School, Brigham and Women's Hospital, Boston, MA,

⁴Department of Anesthesiology, University of Minnesota, Minneapolis, MN, USA

Abstract

Enhanced recovery after surgery protocols are multimodal perioperative care pathways designed to achieve early recovery in patients after surgical procedures by defining and maintaining preoperative organ function and minimizing the profound stress response following surgery. Enhanced recovery protocols have primarily been studied for major abdominal surgeries, however, the knowledge acquired from studying these protocols has facilitated treating patients in ambulatory settings. The key components of enhanced recovery protocols include preoperative counseling, preoperative nutrition, altering the standard perioperative fasting guidelines, and the value of carbohydrate loading up to 2 hours preoperatively, standardized analgesic, and anesthetic regimens (epidural and nonopioid analgesia) and early mobilization. A PubMed search was performed with the following key words: multimodal analgesia, enhanced recovery, ambulatory care, pain management, and opioids. We discuss the use of enhanced recovery protocols and multimodal pain care plans in the ambulatory setting.

Keywords: Ambulatory care, enhanced recovery, multimodal analgesia, opioids, pain management

Introduction

The number of ambulatory surgeries has increased in the United States since the early 1980s.^[1] According to the National Center for Health Statistics (NCHS) data in 2010, 48.3 million surgical and nonsurgical procedures were performed during 28.6 million ambulatory surgery visits to hospitals and Ambulatory Surgery Centers (ASCs) combined. Two important reasons for this increase include development and expansion of minimally invasive and noninvasive procedures (e.g., laparoscopy, endoscopy, and laser surgeries) and the medical and technological advancements in both anesthesia care and analgesia for the relief of pain.^[1]

The Enhanced Recovery After Surgery (ERAS)[®] society was established in 2001. The mission of the ERAS Society is to enhance perioperative care and to improve recovery through research, education, audit, and implementation of evidence-based practice. ERAS has further been described as a systems process involving each aspect of the surgical journey that could affect recovery, ranging from preoperative evaluation and planning to intraoperative surgical and anesthetic techniques, and postoperative care. The main goals of ERAS pathways focus on preoperative nutrition, preoperative optimization, avoidance of prolonged fasting, multimodal analgesic regimens, regional anesthetic techniques, and resumption of diet and mobilization in the early postoperative period. The ERAS Society has published comprehensive guidelines for various surgeries, and when

Address for correspondence: Dr. Alan David Kaye,
Department of Anesthesia, LSUHSC, 1542 Tulane Avenue,
Suite 659, New Orleans, LA 70112, USA.
E-mail: akaye@lsuhsc.edu

Access this article online

Quick Response Code:



Website:
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DOI:
10.4103/joacp.JOACP_51_18

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How to cite this article: Kaye AD, Urman RD, Rappaport Y, Siddaiah H, Cornett EM, Belani K, *et al.* Multimodal analgesia as an essential part of enhanced recovery protocols in the ambulatory settings. *J Anaesthesiol Clin Pharmacol* 2019;35:S40-5.

ERAS protocols are effectively implemented, they help to improve patient safety and quality of surgical care.^[2]

One of the most important components of ERAS is multimodal opioid-sparing analgesia. This is possible because various analgesic regimens and techniques can be employed to target multiple central and peripheral pain pathways and act synergistically to improve the analgesic effect and reduces the doses of any single analgesic agent. ERAS protocols use a standardized multimodal analgesic regimen that includes nonopioids, regional anesthetic techniques to minimize the use of perioperative opioids, and decrease their adverse effects with a goal of an expedited patient recovery after surgery. Nonopioids that are commonly used in ERAS protocols include nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, gabapentin, glucocorticoids, ketamine, and tramadol. The regional anesthetic techniques commonly used in ERAS pathways include neuraxial techniques (epidural, spinal) and peripheral nerve blocks (transversus abdominal plane [TAP], paravertebral, brachial plexus, sciatic, and femoral nerve blocks).

Pain Treatment in Ambulatory Setting

Opioids were the primary antinociceptive modality for anesthesiologists for decades, regardless of the surgical setting. However, with the emergence of the national opioid crisis, there has been a paradigm shift in healthcare encouraging a decrease in opioid use. There is a well-defined trend to minimize opioid use and pursue alternative multimodal pain control approaches, even in patients undergoing long and complicated procedures requiring inpatient stay. Atop of well-known opioid side effects, it has been demonstrated that even a single administration of opioid puts the patient at a risk of developing addiction. Additionally, there is an emerging number of studies unveiling the unique phenomenon of opioid-induced hyperalgesia that have been shown to contribute to morbidity, mortality, prolonged hospitalization, and development of chronic pain. Still, the need for fast patient recovery demands ever more judicious use of opioids and a focus on implementation of opioid-sparing analgesia.^[3,4]

Undertreated pain remains a serious problem for the ambulatory environment and is virtually the biggest constraint for meeting patient discharge criteria. In fact, postoperative hemorrhage, acute pain, dehydration, and fever are all commonly cited reasons for postoperative readmission rates.^[5] Hence, there is a continuous need for a novel, safe, antinociceptive regimen that is devoid of common side effects. Recent data suggest that over 80% of patients have different degrees of postoperative pain, 20% of which claimed their

pain as severe or unbearable.^[6] The situation seems to be even worse in the outpatient sector. Many painful procedures, including a large proportion of orthopedic instrumentations, are shifting to the ambulatory environment. Several studies have estimated moderate-to-severe pain scores as high as 30% in the 24 hours after surgery.^[7,8] The solution to this is proper preoperative patient preparation including starting of the required postoperative physical therapy, use of preemptive nonopioid analgesics, use of regional analgesics including local infiltration, continuation of local anesthetics via catheter use and a protocol of timely use of oral non-opioid analgesics. A discussion on this approach is outlined below.

Understanding the long-term effects of inadequately treated pain and late postoperative physiology are also of great importance. It is not uncommon that patients may initially meet discharge criteria and be successfully released to self-care but will later develop aggravation of their pain level after the effects of residual analgesics wear off. This pain may limit mobility which then further contributes to already existing vicious circuit of stress-induced imbalances. Muscle wasting may result in thrombi formation and immobility creates a favorable environment for the development of pulmonary complications. While it is feasible to foresee these events with an inpatient population, it is not always possible to implement adequate prophylaxis in the outpatient environment due to lack of resources and patient noncompliance. Pain-associated sleep deprivation may additionally contribute to anxiety and depression in patients. Thus, not only is it important to treat immediate postoperative pain, it is also crucial to prevent postdischarge pain flare-ups. Chronic postsurgical pain (CPSP) is a well-established problem which is rarely taken into account by the anesthesia team and represents a persistent pain that lasts over 3–6 months after the procedure. Epidemiological studies have estimated that CPSP occurs roughly after 10%–50% of all surgical procedures, including a proportion of outpatient operations.^[9] Significant progress has been made in understanding what causes the phenomenon of central sensitization.^[10] Tissue injury alone does not activate central sensitization; however, other intraoperative perturbations including retraction, direct neural damage, postprocedural inflammation, and additional subthreshold synaptic impulses are well-defined neuromodulators that contribute to the intensification of pain and development of chronic pain later. An inflammatory pain hypersensitivity theory has been proposed, which postulates that stimulation of COX-2 release leads to PGE2 formation, which, in turn, blocks inhibitory glycinergic receptors allowing for unopposed pain stimuli transmission.^[11]

Identification of individual patient needs (including high-risk patients for intractable postoperative pain, incorporating

patients with a history of hyperalgesia, substance abuse, and opioid dependence) and setting standards for pain treatment is an essential mission of treating pain in the ambulatory setting. Along with type and duration of the surgery, it has been demonstrated that age, gender, and body mass index (BMI) also play a role in the degree of postoperative pain. Young male patients with a higher BMI undergoing orthopedic procedures have been shown to be at the highest risk for severe pain. It is crucial to understand that pain is individual and cannot be a subject to standardized thresholds or always correlate to the extent of surgical intervention. Finally, there should be a clear distinction between different components of social-psychobiological discomforts that can create an unpleasant perioperative experience. They include surgical nociception, other sources of pain and emotional suffering. Therefore, to comply with fast-track nature of ambulatory surgery, it is imperative to treat perioperative pain as a multifactorial problem and recognize unique patient's challenges early to facilitate optimum pain control and fast discharge.

Multimodal Analgesia Treatments

The concept of multimodal anesthesia entails usage of several therapies with distinctive mechanisms of action throughout the preoperative, intraoperative, and postoperative periods to generate pharmacological and clinical synergism and maximize beneficial effects of a single drug or intervention while minimizing their individual side effects.^[12] Various multimodal protocols have been advocated as a solid foundation for effective fast-track surgery.^[13]

Despite the ongoing debate on the ill-effects of opioids and the recent emergence of the opioid crisis, this class of medications remains the mainstay of intraoperative analgesia as no other alternative can offer similar effectiveness. Balanced use of short-acting opioid medications is acceptable. On the contrary, it is a common trend to minimize the postoperative use of long-acting opioids when possible. Therefore, several agents alone or in combination have been well studied in regards to their postoperative opioid sparing and pain reduction properties. To better understand the physiological alterations that result from pain formation, we suggest grouping the currently available agents based on their site of action and role in the disruption

of pain signal formation and propagation [Table 1]. We grouped agents based on the following categories: agents that prevent central sensitization, agents that prevent peripheral sensitization, membrane stabilizers, and agents that act on descending modulation.

Ketamine is an *N*-methyl-D-aspartate (NMDA) antagonist and has been on the market since the mid-20th century. Ketamine has recently gained a resurgence of interest among anesthesiologists as an effective opioid adjunct after NMDA receptors were found to play an important role in central sensitization formation. A recent systematic review on low-dose ketamine use with standard opioid administration showed an overall decrease in opioid use and led to improved quality of pain, with no reported serious side effects.^[14] A subgroup analysis also indicated that the greatest benefit regarding opioid-sparing occurred when high postoperative pain scores were anticipated. Of note, several studies revealed positive effects of ketamine in specific patient populations, including those with chronic pain and opioid dependency.^[15]

Gabapentin is primarily known as an antiepileptic drug and was introduced in 1993. It has been studied and used by many clinicians as a part of multimodal therapy. It inhibits presynaptic voltage-gated calcium channels in the dorsal root ganglia and spinal cord. These channels are known to be upregulated in the event of surgical trauma. Inhibition of these channels shuts down the release of excitatory neurotransmitters. Although there is still no well-established consensus on the optimal dose and time frame for administration, many systematic reviews show its overall positive opioid-sparing effect and reduction of postoperative pain levels, especially in high risk for severe postoperative pain population.^[16] Evidence shows that both drugs (gabapentin and pregabalin) are effective and should be administered at least 2 hours prior to surgery for maximal benefit. Large doses of gabapentin should be avoided due to concern for respiratory depression.

Alpha-2 agonist agents possess anesthesia-favorable pharmacological properties (sedation, hypnosis, anxiolysis, sympatholysis, and analgesia) that make them appropriate adjuvants to a multimodal pain regimen. The antinociceptive effect results from stimulation of α_2 -adrenoreceptors that are located both in the spinal cord and supraspinal region. It has

Table 1: Evidence-based therapy for prevention and treatment of postoperative pain

Agents that prevent central sensitization	Agents that prevent peripheral sensitization	Membrane stabilizers	Agents that act on descending modulation
NMDA antagonists Voltage gated Ca channel blockers Alpha-2 agonists	NSAIDs Acetaminophen Corticosteroids	Voltage Gated Na channel blockers	Serotonin reuptake inhibition drugs

NMDA=*N*-methyl-D-aspartate, NSAID=Nonsteroidal anti-inflammatory drug

been demonstrated that both clonidine and dexmedetomidine reduce opioid consumption after surgery, with the latter being more effective.^[17] Interestingly, the antinociceptive effect is more profound compared with acetaminophen, but when compared with ketamine and NSAIDs the antinociceptive effect is less profound.^[18] Both drugs are known to negatively affect hemodynamics, including their propensity to cause bradycardia and hypotension.

Intravenous administration of membrane-stabilizing agents has been traditionally associated with their antiarrhythmic effect, as blocking the sodium channels would stabilize cell membranes and prevent ectopic discharge. As was recently discovered, the same mechanism is a great contributor to neuropathic pain formation. Intravenous infusion of lidocaine was suggested as an analgesic adjuvant a long time ago; however, this approach has only recently gained popularity. Lidocaine also has analgesic, antihyperalgesic, and anti-inflammatory properties. Although there is not enough data to advocate for comprehensive recommendations, it has been shown that lidocaine infusion is beneficial in abdominal surgery populations. It was associated with shorter hospital stay, faster bowel function return, and lower rates of nausea and vomiting.^[19] It is also thought to have a mild NMDA inhibition effect. More research is needed to confirm safety (as IV lidocaine is known to affect coagulation, fibrinolysis, and platelet aggregation) and optimal dosing, and identify other groups of patients who may potentially benefit from this regimen.

The more familiar and clinically relevant arena of lidocaine and other local anesthetics use includes neuraxial and peripheral nerve blocks. Regardless of the route, regional techniques show strongly positive effects by suppressing postoperative pain and opioid consumption. Furthermore, the use of adjuvant agents in neuraxial and peripheral nerve blocks are useful in preventing prolonged patient pain and decreasing patient narcotic consumption. Adjuvants including epinephrine and clonidine can enhance local anesthetic clinical utility. Dexmedetomidine prolongs regional blockade duration effects. Magnesium prolongs regional block duration but more studies are necessary before this can be recommended as a standard treatment. Tramadol yields inconsistent results and ketamine is associated with psychotomimetic adverse effects.^[20] Buprenorphine consistently increases regional block duration and reduce opioid requirements by a significant amount. Future studies are warranted to define best practice strategies for these adjuvant agents.^[20]

It is now evident that perioperative administration of regional anesthesia is not only a temporizing measure for pain control but it also complies well with the concept of preventive analgesia. A recent systemic review reported an almost universal decrease

in postoperative pain scores that are well beyond the duration of actions of subsequent local anesthetics.^[21]

Agents that are exerting their antinociceptive effects mostly at the peripheral sites by decreasing the release of proinflammatory and pain-augmenting mediators are acetaminophen and non-steroidal anti-inflammatory agents (NSAIDs, including COX-2 selective inhibitors). Postoperative administration of these medications leads to a decrease in 24-h morphine consumption. There is no consistent evidence in the literature favoring one group over the other.^[22] Acetaminophen is traditionally thought to be slightly less effective in pain reduction, whereas NSAIDs are associated with increased bleeding risk, negative GI influence, and other rather controversial and not universally proven side effects, including delayed bone healing. Of note, existing evidence also suggests that when combining acetaminophen and NSAIDs one can achieve more superior analgesia than with either drug alone, signifying synergistic effect.^[23] Intravenous acetaminophen has recently made a reappearance to the market and is a practical alternative if the patient is unable to tolerate oral intake. While there is not enough evidence in the literature to support the advantage of IV acetaminophen over an oral analog, giving it IV does minimize the first pass hepatic effect of oral acetaminophen. Perioperative use of systemic steroids seems to contribute to the opioid-sparing effect and the reduction of postoperative pain scores, in addition to their well-known antiemetic properties.^[24] Pain reduction effect seems to be dose independent. Moreover, no significant side effects including increased risk of wound infections rate or alterations in wound healing have been reported. The benefits of perioperative administration of selective serotonin reuptake inhibitors are under investigation, but no clinical significance has been yet reported. More research is needed.

Enhanced Recovery after Surgery Protocols

Preoperative Enhanced Recovery after Surgery protocols

Preoperative nutrition

Inadequate nutrition has been identified as a risk factor for increased mortality and morbidity in patients undergoing surgery. A recent study demonstrated that nutritional deficiency preoperatively is a strong predictor of 90-day mortality and poor overall survival.^[25] Hence, the assessment and treatment of poor nutrition has become an essential component of the ERAS protocol. Furthermore, prolonged parenteral nutrition or combination of parenteral and enteral nutrition may be needed to correct preoperative nutritional deficiencies. Input from a dietician or nutritionist might be helpful.

Carbohydrate loading

It is well known that the body's response to surgery results in a catabolic state. ERAS protocols aim to attenuate this catabolic response. In this state, increased cortisol levels stimulate gluconeogenesis and glycogenesis in the liver. As such, there is insulin resistance due to alpha-2-adrenergic inhibition of pancreatic B cells. Hyperglycemia contributes to poor wound healing and increased risk of infections. To offset the effects of insulin resistance, adequate pain control, avoidance of a prolonged fasting period, and the use of carbohydrate loading are recommended.

Preoperative fasting leads to increased insulin resistance and hyperglycemia; hence, shortening the duration of preoperative fasting not only reduces insulin resistance but also reduces protein breakdown and improves muscle function.

Studies comparing different perioperative fasting regimens and perioperative complications showed no evidence of increased risk of aspiration with a shortened fluid fast.^[26] Carbohydrate loading has been shown to decrease insulin resistance; protein breakdown improves muscle function and reduces preoperative thirst, hunger, and anxiety.

Mechanical bowel preparation

The main goal of MBP is to reduce the large bowel of solid fecal contents and lower bacterial load; however, MBP leads to liquefying solid feces which may increase the risk of intraoperative spillage. MBP can also result in a higher incidence of post-operative ileus, slower commencement of diet, greater risk of wound dehiscence, and longer hospital stay.

Intraoperative Enhanced Recovery after Surgery protocols

Use of short-acting anesthetic agents, avoidance of salt and water overload, and maintenance of normothermia using a body warmer and a fluid warmer have all been shown to decrease patient complications when incorporated into an intraoperative ERAS protocol.^[27]

Postoperative Enhanced Recovery after Surgery protocol

Postoperative nutrition

Early postoperative nutrition can reduce insulin resistance that is associated with surgery, prevent protein breakdown, and improve muscle function. Recent evidence has found no benefit to keeping patients NPO postoperatively. Early feeding actually results in a lowered incidence of anastomotic dehiscence, wound infection, pneumonia, and intra-abdominal abscess.^[28]

Prevention of postoperative ileus

Bowel function is dependent on factors including enteric and central nervous systems, hormonal influences, neurotransmitters, and local inflammatory pathways. Opioids, intraoperative fluid resuscitation, surgical stress, and bowel handling can disrupt the factors responsible for normal balance and lead to postoperative ileus. Factors, which help reduce the incidence of postoperative ileus, include gentle tissue handling, epidural anesthesia, minimally invasive surgery, avoiding of fluid overload, and early feeding.

The use of multimodal opioid-sparing analgesia should be a priority postoperatively. Use of NSAIDs, acetaminophen, ketamine, and glucocorticoids along with regional anesthetic techniques should be encouraged. Early mobilization and early removal of catheters also are part of ERAS protocol.^[29,30]

A number of European countries have implemented ERAS protocols in their healthcare models. The United States implementation of ERAS protocols by hospitals has been challenging. There are several possible reasons for this challenge including lack of awareness among anesthesiologists and the realization that the process of implementing ERAS has many barriers. There are also concerns of the liability associated with initiating something new, resistance to new ideas, and that ERAS does not apply to anesthesia.

However, ASA supports the concept of the Perioperative Surgical Home (PSH) model of care and ERAS can form a clinical core of the PSH initiative.^[31]

Conclusion

ERAS protocols have been referred to as "optimized patient care" or "fast-track surgery". ERAS protocols and programs lead to improved patient outcomes, reduced rates of complications, shorter inpatient stays, and significant cost-savings. ERAS protocols have primarily been studied for major abdominal surgeries; however, the knowledge acquired from studying these protocols has facilitated treating patients in ambulatory settings. Although more research is needed to prove the efficacy of ERAS protocols, evidence from existing studies have shown that such protocols significantly reduce postoperative hospital stay without increasing morbidity and mortality, in turn, decreasing hospital costs and also increasing patient satisfaction.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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